



## Patients with the Diagnosis of Malignancy Followed Up with Candidemia in a Tertiary University Hospital: Analysis of Species and Resistance

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### Research Article

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#### ABSTRACT

**Introduction:** The incidence of Candidemia, which is a significant cause of morbidity and mortality, is increasing. Patients with a diagnosis of malignancy, who use immunosuppressants, and who require follow-up in the intensive care unit are at high risk for Candidemia. The incidence and resistance patterns of Candida species may vary depending on population, geographical location, and previous antifungal exposure. It was aimed to identify Candida spp. isolated from blood culture samples of patients diagnosed with malignancy for the species level, and to determine their antifungal drug susceptibility, in this study.

**Materials and Methods:** In this study, the results of the samples with growth in blood cultures between January 2016 and July-2022 were examined retrospectively. The patients with a diagnosis of Candida spp. fungal growth in at least one blood culture set during hospitalization and the patients with a diagnosis of malignancy defined as candidemia and treated with antifungal were included in the study.

**Results:** Candida albicans growth was detected in 43.5% (10) of the blood cultures included in the study. Non-albicans species were isolated in a total of 13 blood cultures (56.5%): 30.4% (7) C. parapsilosis; 17.4% (4) C. glabrata; 4.3% (1) C. tropicalis; 4.3% (1) C. krusei. Very low resistance rates were determined against many antifungals such as Amphotericin B (0%), Micafungin (0%), Fluconazole (10%), Posaconazole (0%), Voriconazole (0%), and Anidulafungin (25%) for C. albicans isolates in our study. On the other hand, higher levels of resistance were observed for almost all antifungals for non-albicans species, the incidence of which has increased in recent years.

**Discussion and Suggestions:** The epidemiology of Candida infections has been changing in recent years. Although C. albicans is still the main reason for invasive Candidiasis in many clinical environments, a significant number of patients are now infected with non-albicans Candida species. Candida species may show differential susceptibility to commonly used antifungal agents. The susceptibility of Candida species to commonly used antifungal agents varies. As in our study, we believe that following the epidemiological data and antifungal susceptibility patterns of medical centers will allow effective empirical treatment and improve Candidemia prognosis.

**Keywords:** Candidemia, Blood Culture, Malignancy, Antifungal Resistance

## Üçüncü Basamak Bir Üniversite Hastanesinde Kandidemi ile Takip Edilen Malignite Tanılı Hastalar: Tür ve Direnç Analizi

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#### Öz

**Giriş:** Önemli bir morbidite ve mortalite nedeni olan kandidemi insidansı artış göstermektedir. Malignite tanısı olan, immünsüpresan kullanan ve yoğun bakımda takip edilmesi gereken hastalar kandidemi açısından yüksek risk altındadır. Candida türlerinin sıklıkları ve direnç paternleri ilgili popülasyona, coğrafi bölgeye, önceki antifungal maruziyete bağlı olarak değişebilmektedir. Bu çalışmada malignite tanılı hastaların kan kültürü örneklerinden izole edilen Candida cinsi mayaların tür düzeyinde tanımlanmasını ve antifungal ilaç duyarlılıklarının belirlenmesi amaçlanmıştır.

**Gereç ve Yöntem:** Çalışmada, Ocak 2016 ile Temmuz 2022 tarihleri arasında kan kültürlerinde üreme olan örneklerin sonuçları geriye dönük olarak incelenmiştir. Hastane yatışı sırasında en az bir kan kültürü setinde Candida cinsi mantar üremesi olan ve kandidemi olarak değerlendirilip antifungal tedavi uygulanan malignite tanılı hastalar çalışmaya dahil edilmiştir.

**Bulgular ve Tartışma:** Çalışmaya dahil edilen kan kültürlerinin %43.5'inde (10) Candida albicans üremesi olmuştur. Toplam 13 kan kültüründe (%56.5) ise albicans dışı türler izole edilmiş olup bunların dağılımı %30.4 (7) C. parapsilosis, %17.4 (4) C. glabrata, %4.3 (1) C. tropicalis, %4.3 (1) C. krusei şeklindedir. Çalışmamızda C. albicans izolatları için Amfoterisin B (%0), Mikafungin (%0), Flukonazol (%10), Posakonazol (%0), Vorikonazol (%0) ve Anidulafungin (%25) gibi birçok antifungale karşı oldukça düşük direnç oranları tespit edilmiştir. Diğer yandan, son yıllarda sıklığı artış gösteren albicans dışı türler için hemen tüm antifungaller açısından daha yüksek direnç düzeyleri gözlenmiştir.

**Sonuçlar:** Candida enfeksiyonlarının epidemiyolojisi son yıllarda değişmektedir. C. albicans, çoğu klinik ortamda hala invaziv kandidiyazisin ana nedeni olmasına rağmen, hastaların önemli bir kısmı artık albicans dışı Candida türleri ile enfektir. Candida türleri sık kullanılan antifungal ajanlara karşı farklı duyarlılıklar gösterebilmektedir. Çalışmamızda olduğu gibi, merkezlerin kendi epidemiyolojik verilerini ve antifungal duyarlılık paternlerini takip etmesinin etkin ampirik tedaviye fırsat vereceği ve kandidemi prognozunda iyileşme sağlayacağı kanısındayız.

**Anahtar sözcükler:** Kandidemi, Kan Kültürü, Malignite, Antifungal Direnç

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## Introduction

Invasive Candidiasis (IC) is a general term that refers to a group of infectious syndromes caused by different species of *Candida*. Candidemia is the most commonly known syndrome associated with IC. Candidemia is the main cause of morbidity and mortality. Due to the increased comorbidity of patients, the incidence of candidemia is increasing<sup>1</sup>. Patients with a diagnosis of malignancy, who use immunosuppressants, and who require follow-up in the intensive care unit are at high risk for IC. These patient groups differ from the general population in terms of species and resistance profile<sup>2,3</sup>.

The incidence and resistance patterns of *Candida* species vary depending on population, geographical location, and previous anti-fungal exposure<sup>4</sup>. Rapid identification of *Candida* species and the starting of an accurate and effective treatment in the early stages of the disease according to antifungal susceptibility test results will positively affect the prognosis of the disease<sup>5</sup>.

It is very important for each medical center to analyze its own-resistance patterns, as there may be differences in outcomes between medical centers for antifungal susceptibility test results. It was aimed to identify the species level of *Candida spp.* isolated from blood culture samples of patients with diagnoses of malignancy to determine their antifungal drug susceptibility in this study.

## Materials and Methods

This study was conducted with the approval of the Sivas Cumhuriyet University Non-Invasive Clinical Research Ethics Committee (Date: 21.09.2022 and Decision No: 2022-09/21). In this study, the results of the samples with culture-growth in blood culture bottles sent to Sivas Cumhuriyet University Health Services Application and Research Hospital Microbiology Laboratory between January 2016 and July 2022 were retrospectively analyzed from the laboratory and hospital information system.

The patients with a diagnosis of *Candida spp.* fungal growth in at least one blood culture set during treatment in Hematology, Medical Oncology, Surgical Oncology Services, and Anesthesia Intensive Care Unit, and the patients with a diagnosis of malignancy defined as candidemia and treated with antifungal were included in this study. *Candida* growth was not evaluated as colonization in any of the blood cultures. The first fungal agent isolated from one patient was included in the study. Repeated isolates from the same patient were not included in the study.

The blood samples were inoculated into BD BACTEC Plus Aerobic/F (Becton Dickinson, Sparks, USA) culture bottles according to the producer

company's recommendations. The samples were then incubated in the BD BACTEC 9120 (Becton Dickinson, Sparks, USA) culture device. Subculture passages were sub-passed on blood agar and Sabouraud dextrose agar (SDA) media from the bottles in which the device gave a growth signal and incubated in an incubator for 24-48 hours. The germ tube tests of the produced *Candida* strains were performed. The isolates were identified by the Bruker IVD MALDI Biotyper 2.3 (Bruker Daltonik GmbH, Bremen, Germany) instrument based on matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS).

Antifungal susceptibility tests for '*Amphotericin B*, *Fluconazole*, *Itraconazole*, *Posaconazole*, *Voriconazole*, *Anidulafungin*, *Micafungin*' antifungals were performed by colorimetric broth-microdilution method (Sensititre Yeastone®, Trek Diagnostic Systems, Thermo Scientific, East Grinstead, West Sussex, UK). *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258 were included as control strains in all studies. The Minimum Inhibitory Concentration (MIC) values were determined after 24 hours of incubation at 34–35°C. The antimicrobial susceptibilities were evaluated following the recommendations in the EUCAST (The European Committee on Antimicrobial Susceptibility Testing) guidelines for the relevant period<sup>6</sup>.

SPSS program (Statistical Package for the Social Sciences) version 22.0 (IBM Corp., Armonk, NY, USA) was used for the evaluation of the data obtained from the study. The results are expressed as mean ± standard deviation for continuous variables, and as the number of cases and percentage (%) for nominal variables.

## Results and Discussion

The 23 patients diagnosed with malignancy were included in this research whom *Candida spp.* fungal growth was observed in cultures in their blood culture bottles which were sent from Hematology, Medical Oncology, Surgical Oncology services, and Anesthesia Intensive Care Unit to Sivas Cumhuriyet University Health Services Application and Research Hospital Microbiology Laboratory, between January 2016 and July 2022. The data related to the research were obtained by retrospectively scanning the hospital and laboratory information system. The mean age of the analyzed patients was 60.65 ± 9.65 (age range: 41-81 years). 26% of the patients are female. The samples were sent from 34.8% (8) Medical Oncology, 30.4% (7) Hematology, 21.7% (5) Surgical Oncology, and 13% (3) Anesthesia and Intensive Care Unit. Fungal growing of *Candida spp.* was observed in at least one blood culture set for all patients. *Candida albicans* grew in 43.5% (10) of the isolated samples.

From other samples (56.5%), non-albicans species were isolated. The distribution of these species is as follows: 30.4% (7) *C. parapsilosis*, 17.4% (4) *C.*

*glabrata*, 4.3% (1) *C. tropicalis*, 4.3% (1) *C. krusei*. The distribution of these species by year is shown in Table 1.

**Table 1.** Distribution of *Candida* species by years

Species	2016	2017	2018	2019	2020	2021	2022
<i>Candida albicans</i>	5	2	1	1	0	0	1
<i>Candida parapsilosis</i>	0	0	0	0	2	5	0
<i>Candida glabrata</i>	0	1	1	0	1	0	1
<i>Candida tropicalis</i>	0	0	0	0	1	0	0
<i>Candida krusei</i>	0	1	0	0	0	0	0
TOTAL	5	4	2	1	4	5	2

*Candida albicans* is still the most common *Candida* species to cause Candidemia in our hospital, as reported by most medical centers. However, there has been an increase in non-albicans *Candida* species in recent years. It is

thought that this new increasing is due to the natural selection process of resistant strains to the antifungals used in treatment <sup>7</sup>. The malignancy diagnoses and hospitalization units of the patients are shown in Table 2.

**Table 2.** Malignancy diagnoses and hospitalization units of the patients and causative *Candida* species

Hospitalization units	<i>Candida</i> species	Malignancy diagnoses
Medical oncology	<i>C. albicans</i>	Lung cancer
Medical Oncology	<i>C. glabrata</i>	Pancreatic cancer
Medical Oncology	<i>C. parapsilosis</i>	Breast cancer
Medical Oncology	<i>C. glabrata</i>	Lung cancer
Hematology	<i>C. albicans</i>	Acute lymphoblastic leukemia
Surgical Oncology	<i>C. albicans</i>	Gastric cancer
Medical Oncology	<i>C. albicans</i>	Lung cancer
Anesthesia Intensive Care Unit	<i>C. parapsilosis</i>	Maxillary sinus tumor
Hematology	<i>C. parapsilosis</i>	Diffuse Large B-Cell Lymphoma
Medical Oncology	<i>C. tropicalis</i>	Colon cancer
Hematology	<i>C. krusei</i>	Chronic lymphocytic leukemia
Surgical Oncology	<i>C. albicans</i>	Pancreatic cancer
Hematology	<i>C. albicans</i>	Diffuse Large B-Cell Lymphoma
Surgical Oncology	<i>C. parapsilosis</i>	Colon cancer
Hematology	<i>C. albicans</i>	Multiple Myeloma
Medical Oncology	<i>C. albicans</i>	Breast cancer
Hematology	<i>C. glabrata</i>	Multiple Myeloma
Surgical Oncology	<i>C. glabrata</i>	Pancreatic cancer
Anesthesia Intensive Care Unit	<i>C. parapsilosis</i>	Lung cancer
Medical Oncology	<i>C. albicans</i>	Lung cancer
Anesthesia Intensive Care Unit	<i>C. parapsilosis</i>	Rectal cancer
Hematology	<i>C. albicans</i>	Acute myeloid leukemia
Surgical Oncology	<i>C. parapsilosis</i>	Colon cancer

As reported by many medical centers in our study too, acute leukemia and lymphoma are the most common hematological malignancies

associated with candidemia, and gastrointestinal cancers are the most common solid tumors <sup>8,9</sup>. Candidemia is a very difficult clinical condition with

high morbidity and mortality rates. The essential determinant of survival in this disease is early recognition of the disease and timely initiation of appropriate systemic antifungal therapy. For these reasons, it is very important for each medical center to follow its own epidemiological data and patterns of antifungal susceptibility<sup>10</sup>. Patients' antifungal susceptibility results are shown in Table 3 who

diagnosed with malignancy *Candida spp.* fungal growth was observed in cultures in their blood culture bottles which were sent from Hematology, Medical Oncology, Surgical Oncology services, and Anesthesia Intensive Care Unit to Sivas Cumhuriyet University Health Services Application and Research Hospital Microbiology Laboratory, between January 2016 and July 2022.

**Table 3.** Antifungal susceptibility of *Candida* fungi isolated in blood cultures of patients with malignancy

Species (n)	AB		AND		MF		FZ		IZ		PZ		VOR		
	S	R	S	R	S	R	S	R	S	I	R	S	R	S	R
<i>C. albicans</i> (10)	10 (100)	0	6 (75)	2 (25)	7 (100)	0	9 (90)	1 (10)	4 (50)	3 (37.5)	1 (12.5)	3 (100)	0	4 (100)	0
Non-albicans <i>Candida</i> (13)	12 (92.3)	1 (7.7)	8 (72.7)	3 (27.3)	10 (100)	0	5 (45.5)	6 (54.5)	1 (12.5)	0	7 (87.5)	1 (12.5)	7 (87.5)	3 (37.5)	5 (62.5)
<i>C. parapsilosis</i> (7)	7 (100)	0	6 (85.7)	1 (14.3)	6 (100)	0	3 (42.9)	4 (57.1)	1 (14.3)	0	6 (85.7)	1 (14.3)	6 (85.7)	3 (42.9)	4 (57.1)
<i>C. glabrata</i> (4)	4 (100)	0	2 (66.7)	1 (33.3)	4 (100)	0	2 (66.7)	1 (33.3)	-	-	-	-	-	-	-
<i>C. tropicalis</i> (1)	1 (100)	0	0	1 (100)	-	-	0	1 (100)	0	0	1 (100)	0	1 (100)	0	1 (100)
<i>C. krusei</i> (1)	0	1 (100)	-	-	-	-	-	-	-	-	-	-	-	-	-
<b>TOTAL</b> (23)	<b>22</b> (95.7)	<b>1</b> (4.3)	<b>14</b> (73.7)	<b>5</b> (26.3)	<b>17</b> (100)	<b>0</b>	<b>14</b> (66.7)	<b>7</b> (33.3)	<b>5</b> (31.3)	<b>3</b> (18.7)	<b>8</b> (50)	<b>4</b> (36.4)	<b>7</b> (63.6)	<b>7</b> (58.3)	<b>5</b> (41.7)

AB: Amphotericin B, AND: Anidulafungin, MF: Micafungin, FZ: Fluconazole, IZ: Itraconazole, PZ: Posaconazole, VOR: Voriconazole, S: Susceptible, I: Susceptible, increased exposure, R: Resistant.

In a study reported from our hospital in 2019, the most frequently detected *Candida* infection was found to be the urinary system infection followed by Candidemia. In 66% of all *Candida* infections, *Candida albicans* was identified as the causative microorganism<sup>11</sup>.

In a study reported from Portugal in which cases followed up with Candidemia in a tertiary hospital were analyzed, *Candida albicans* (51.3%) was the most isolated species, similar to our results. However, the second most common causative microorganism isolated in this study was *C. glabrata*, unlike our study<sup>12</sup>. In a study conducted at a tertiary academic hospital in Greece, *Candida albicans* (41%), followed by *Candida parapsilosis* (37%), was the most common species. These results and rates are similar to our study<sup>13</sup>.

In a study about the epidemiology and susceptibility of Candidemia conducted in Israel, *Candida albicans* was reported as the prominent pathogen (39.4%). However, it has been noted that the results have shifted towards non-albicans *Candida* species. *Candida glabrata* (40%) was determined as the dominant species among these species. Few of the *Candida albicans* isolates were found resistant to Fluconazole (3.3%). A high resistance rate (37.8%) was detected in *Candida parapsilosis* isolates<sup>14</sup>.

In a study of adult patients with malignancies from Taiwan, non-albicans Candidemias were analyzed, and *Candida tropicalis* was the most

common species (41.9%). In addition, it was stated that *C. tropicalis* had the highest resistance rate (13.9%) against fluconazole among all isolates in this study<sup>15</sup>. *C. tropicalis*, which was isolated in our study, is also a resistant strain.

Fluconazole, an azole structure, is the most widely used antifungal drug due to its low host-toxicity, high solubility in water, and high bioavailability<sup>16</sup>. Fluconazole has fungistatic activity only against *Candida* species, and both innate and acquired resistance have been reported<sup>17</sup>. Fluconazole resistance was detected in only one (10%) of the *Candida albicans* isolates in our study. A high Fluconazole resistance (54.5%) was detected in non-albicans isolates. The high resistance rates of these species, which have been widely identified, limit the treatment options.

The multiple antifungal resistance of *C. krusei* and *C. tropicalis* isolates cause concern for our hospital. But the number of our patients is quite limited. Multicenter studies with more patient groups are needed to reveal more accurate results.

## Conclusion

Effective treatment of invasive fungal pathogens is a priority in immunocompromised cancer patients. Given the increased incidence of invasive candidiasis and poor outcomes in patients with malignancies, early diagnosis and treatment are necessary to achieve a better prognosis<sup>18</sup>.

The epidemiology of *Candida spp.* infections has changed in recent years. Although *Candida albicans* remains the major reason for invasive Candidiasis in many clinics, a significant number of patients are now infected with non-*albicans Candida* species. Different *Candida* species have different susceptibilities to commonly used antifungal agents. The management of *Candida* infections is becoming a significant problem due to the development of innate resistance to antifungal therapy in some species and acquired resistance during treatment in other species<sup>19</sup>. It is very important that each medical center monitors its epidemiological data and antifungal susceptibility patterns. In this way, it is thought that empirical treatment can be started early and effectively. We are of the opinion that this situation can provide a significant improvement in the prognosis of the disease.

The first data of this study were presented as an oral presentation at the "3. International Cancer Day – Sivas Cumhuriyet University" on 15.09.2022 as a preliminary study.

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